Concise report

Early progression of atherosclerosis in children with chronic infantile neurological cutaneous and articular syndrome

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Abstract

Objective. Chronic inflammation plays a key role in the development of atherosclerosis. Early progression of atherosclerosis has been reported in patients with RA. Cryopyrin-associated periodic syndromes (CAPS) are autosomal dominant autoinflammatory disorders caused by heterozygous NLRP3 gene mutations. Chronic infantile neurological cutaneous and articular (CINCA) syndrome is the most severe form of CAPS and patients display early onset of rash, fever, uveitis and joint manifestations. However, there has been no previous report on atherosclerosis in patients with CAPS. The objective of this study is to assess the development of atherosclerosis in patients with CINCA syndrome.

Methods. Intima–media thickness (IMT) of the carotid arteries, stiffness parameter $\beta$, ankle brachial index (ABI) and pressure wave velocity (PWV) were evaluated by ultrasonography in 3 patients with CINCA syndrome [mean age 9.0 years (s.d. 5.3)] and 19 age-matched healthy controls [9.3 years (s.d. 4.3)].

Results. The levels of carotid IMT, stiffness parameter $\beta$ and PWV in CINCA syndrome patients were significantly higher than those in healthy controls [0.51 mm (s.d. 0.05) vs 0.44 (0.04), $P = 0.0021$; 6.1 (s.d. 1.7) vs 3.9 (1.0), $P = 0.0018$; 1203 cm/s (s.d. 328) vs 855 (114), $P = 0.017$, respectively].

Conclusion. Patients with CINCA syndrome showed signs of atherosclerosis from their early childhood. The results of this study emphasize the importance of chronic inflammation in the development of atherosclerosis. Further analysis on atherosclerosis in young patients with CINCA syndrome may provide more insights into the pathogenesis of cardiovascular disease.

Key words: ankle–brachial index, atherosclerosis, chronic infantile neurologic cutaneous and articular syndrome, cryopyrin-associated periodic syndromes, intima-media thickness, pulse wave velocity.

Introduction

It is well known that chronic inflammation is a predisposing factor for atherosclerosis. There has been considerable interest regarding the possible causal role of inflammation in the development of atherosclerosis in adult patients with RA, SLE and familial Mediterranean fever (FMF). Patients with SLE, APS or RA have increased mortality rates related to early atherosclerosis. Relative risk of 5 for myocardial infarction, 6–10 for stroke in SLE patients and 3.6 for cardiovascular deaths in RA patients has been reported [1]. Furthermore, the American Heart Association has reported that chronic inflammatory disease is one of the eight high-risk factors for atherosclerosis, even in children [2].

Cryopyrin-associated periodic syndromes (CAPS), including chronic infantile neurological cutaneous and articular (CINCA) syndrome, Muckle–Wells syndrome and familial cold autoinflammatory syndrome, are autosomal dominant autoinflammatory syndromes caused by heterozygous mutations of the *NLR family pyrin domain*
containing 3 (NLRP3) gene. It has been reported that disease-associated NLRP3 mutation causes IL-1β oversecretion by caspase-1 activation. CINCA syndrome, the most severe form among them, is characterized by chronic systemic inflammation manifested as early onset of rash, fever, uveitis, chronic meningitis and joint symptoms [3]. However, there has been no previous report evaluating atherosclerosis in patients with CAPS.

Several physiological examinations are applied to assess atherosclerosis. Carotid intima–media thickness (cIMT) is known to be an indicator of atherosclerosis for adults and children [4]. In fact, increased cIMT has been shown in children with obesity, hyperlipidaemia and diabetes mellitus [5]. It has been reported that stiffness parameter β is more useful in detecting atherosclerotic changes in earlier stages than cIMT [6]. Also, pulse wave velocity (PWV) and ankle–brachial index (ABI) are simplified parameters of the severity of atherosclerosis and predictors of prognosis in adult patients with cardiovascular disease [7, 8]. The objective of this study is to assess the development and progression of atherosclerosis in young patients with CINCA syndrome by measuring cIMT, stiffness parameter β, PWV and ABI.

Patients and methods

Study population

Three patients (a 5-year-old boy [9], a 7-year-old girl [10] and a 15-year-old boy [11]) with CINCA syndrome and 19 age-matched healthy controls were enrolled in this study. NLRP3 mutations were observed in all three patients. The parameters of atherosclerosis were investigated in these three patients who were in remission for 1 year after the initiation of canakinumab treatment. The Institutional Review Board of Kyushu University Hospital approved the study and informed consent was obtained from each subject.

Sonographic study

Carotid artery US was performed with an iE33 ultrasound machine (Philips, Amsterdam, The Netherlands) using an 11 MHz probe. Measurements were obtained with subjects in the supine position by experienced sonographers blinded to the subjects’ clinical status. Ultrasonographic images of the right and left common carotid arteries (CCAs) of each subject at the lower third cervical region proximally and 1 cm above the carotid bulb distally in the longitudinal plane were obtained. CCA IMT measurements of the distal CCA posterior wall were done manually by the distance measurement system of the sonography device after magnification of the images. Three measurements were made in a non-neighbouring fashion within an ~1 cm segment from both the left and right CCA proximal and distal portions. The IMT was measured during end diastole. Mean IMT was calculated as the average of three consecutive measurements of maximum far wall thickness obtained from the CCA. Measurement of the internal diameter of the CCA was performed for three consecutive heartbeats. Intraobserver variability was 1.7% for IMT and 3.1% for arterial wall diameter measurements. The stiffness parameter β was calculated from this formula [12]: $\beta = [\ln(SBP/DBP)]/(\Delta D/D)$, where SBP is the systolic blood pressure, DBP is the diastolic blood pressure, D is carotid artery diastolic diameter and $\Delta D$ is the change in artery diameter during systole.

PWV and ABI

PWV and ABI were measured using a BP-203RPEIII (Omron Colin, Tokyo, Japan). PWV, ABI, the blood pressure of the extremities, ECG and heart sounds were synchronously measured and then automatically recorded. Electrodes were contacted on both wrists and a microphone was attached to the left margin of the sternum. The extremities were then wrapped by cuffs that were connected to a pulse monitor. The volume wave and time difference emitted from the pulse monitor were recorded. The pulse wave was defined as the value obtained by dividing the distance between the two points by the time spent in transferring the pulse. In the current study, the pulse wave was measured in the brachial artery and ankle (baPWV). The ABI was defined as the ratio between the systolic pressure measured in the ankle and that measured in the brachial artery.

Laboratory evaluation

In the morning, after an overnight fast, venous blood was sampled for the measurement of serum concentrations of glucose, total cholesterol, triglycerides and standard CRP.

Statistical analysis

Data are expressed as mean (s.d.). Differences between data were studied using the Student’s t test. Analytical statistics of data between group comparisons of categorical data parameters were performed by using the chi-square test. Statistical significance was taken as $P < 0.05$. All statistical analyses were performed using JMP8 (SAS Institute, Tokyo, Japan).

Results

Clinical characteristics of the study group are presented in Table 1. Age, sex and triglyceride levels were similar between patients with CINCA syndrome and control subjects ($P = 0.65$, 0.53 and 0.17, respectively). Total cholesterol levels in CINCA syndrome patients were significantly lower than those in healthy controls, although they were within normal ranges in both groups. CRP concentrations in the patient group were significantly higher than in healthy controls [5.76 mm (s.d. 2.05) vs 0.08 (0.16), $P < 0.0001$].

All subjects tolerated the sonographic examination well. Sonographic study results and normal values of the parameters for the age of the patients [13, 14] are summarized in Table 2. Carotid artery analysis revealed that the IMT and stiffness parameter β of patients with CINCA syndrome were significantly higher than those of healthy controls [0.51 mm (s.d. 0.05) vs 0.44 (0.04), $P = 0.0021$, and 6.1 (s.d. 1.7) vs 3.9 (1.0), $P = 0.018$, respectively].
The averaged baPWV of the patients was significantly higher than that of controls [1203 cm/s (S.D. 328) vs 855 (114), P = 0.017] (Table 2). There was no significant difference in ABI between the two groups, although the values of two patients were lower than the normal range [15].

Discussion

In the present study we found that patients with CINCA syndrome develop atherosclerosis from early childhood. There have been many previous studies describing atherosclerosis associated with inflammatory diseases such as RA, SLE and FMF [1]. However, this is the first report showing the youngest group of patients who developed atherosclerosis associated with inflammatory disorders.

It has been shown that inflammation plays an important role in the development of atherosclerosis. The presence of macrophages and activated lymphocytes within the plaques supports the nature of an immune system-mediated inflammatory disorder of atherosclerosis. It has been shown that higher disease activity representing higher inflammatory burden is associated with increased cardiovascular events in patients with RA and SLE [16]. It may be induced by elevated inflammatory cytokines, which can cause the development of endothelial dysfunction in atherosclerotic processes. In addition, changes in lipid metabolism and a wide variety of immune and inflammatory alterations that directly affect the endothelium, vascular smooth muscle cells and inflammatory cellular components of the atherosclerotic plaque may also play important roles in the development and progression of atherosclerosis in patients. CINCA syndrome is the most severe form of CAPS, and patients display severe systemic inflammation from the neonatal period [3].

### Table 1 Clinical and laboratory characteristics of the subjects

<table>
<thead>
<tr>
<th></th>
<th>Patient 1</th>
<th>Patient 2</th>
<th>Patient 3</th>
<th>CINCA syndrome (n=3), mean (s.d.)</th>
<th>Controls (n=19), mean (s.d.)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gender, male/female</td>
<td>Male</td>
<td>Female</td>
<td>Male</td>
<td>2/1</td>
<td>9/10</td>
<td>0.53</td>
</tr>
<tr>
<td>Age, years</td>
<td>5</td>
<td>7</td>
<td>15</td>
<td>9.0 (5.2)</td>
<td>9.3 (4.2)</td>
<td>0.65</td>
</tr>
<tr>
<td>BMI, kg/m²</td>
<td>16.0</td>
<td>15.5</td>
<td>16.8</td>
<td>16.1 (0.6)</td>
<td>17.3 (2.9)</td>
<td>0.51</td>
</tr>
<tr>
<td>Systolic blood pressure, mmHg</td>
<td>91</td>
<td>96</td>
<td>128</td>
<td>105 (20)</td>
<td>99 (8)</td>
<td>0.38</td>
</tr>
<tr>
<td>Diastolic blood pressure, mmHg</td>
<td>45</td>
<td>50</td>
<td>68</td>
<td>54 (12)</td>
<td>53 (4)</td>
<td>0.73</td>
</tr>
<tr>
<td>Total cholesterol, mg/dl</td>
<td>123</td>
<td>122</td>
<td>131</td>
<td>125 (5)</td>
<td>159 (17)</td>
<td>0.0046</td>
</tr>
<tr>
<td>Triglycerides, mg/dl</td>
<td>61</td>
<td>79</td>
<td>157</td>
<td>99 (51)</td>
<td>70 (28)</td>
<td>0.17</td>
</tr>
<tr>
<td>Glucose, mg/dl</td>
<td>93</td>
<td>85</td>
<td>102</td>
<td>94 (3)</td>
<td>94 (6)</td>
<td>0.95</td>
</tr>
<tr>
<td>CRP, mg/dl</td>
<td>0.26</td>
<td>1.62</td>
<td>5.55</td>
<td>2.48 (2.75)</td>
<td>0.08 (0.16)</td>
<td>&lt;0.0001</td>
</tr>
</tbody>
</table>

CINCA syndrome: chronic infantile neurological cutaneous and articular syndrome.

### Table 2 Ultrasonographic examination, baPWV and ABI in CINCA syndrome patients and control subjects

<table>
<thead>
<tr>
<th></th>
<th>Patient 1</th>
<th>Patient 2</th>
<th>Patient 3</th>
<th>CINCA syndrome (n=3), mean (s.d.)</th>
<th>Controls (n=19), mean (s.d.)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intima-media thickness, mm (normal value for each age) [13]</td>
<td>0.47 (0.40)</td>
<td>0.5 (0.40)</td>
<td>0.57 (0.50)</td>
<td>0.51 (0.05)</td>
<td>0.44 (0.04)</td>
<td>0.0021</td>
</tr>
<tr>
<td>Systolic diameter, mm</td>
<td>5.5</td>
<td>5.8</td>
<td>5.8</td>
<td>5.7 (0.2)</td>
<td>6.2 (0.8)</td>
<td>0.30</td>
</tr>
<tr>
<td>Diastolic diameter, mm</td>
<td>4.8</td>
<td>5.2</td>
<td>5.4</td>
<td>5.1 (0.3)</td>
<td>5.3 (1.7)</td>
<td>0.63</td>
</tr>
<tr>
<td>Stiffness parameter β (normal value for each age) [14]</td>
<td>4.8 (3.4)</td>
<td>5.7 (3.7)</td>
<td>7.6 (4.5)</td>
<td>6.1 (1.7)</td>
<td>3.9 (1.0)</td>
<td>0.018</td>
</tr>
<tr>
<td>Right baPWV, cm/s</td>
<td>1068</td>
<td>920</td>
<td>1566</td>
<td>1185 (338)</td>
<td>850 (114)</td>
<td>0.0025</td>
</tr>
<tr>
<td>Left baPWV, cm/s</td>
<td>1053</td>
<td>1022</td>
<td>1587</td>
<td>1221 (318)</td>
<td>859 (114)</td>
<td>0.0014</td>
</tr>
<tr>
<td>Averaged baPWV, cm/s (normal value for each age) [15]</td>
<td>1061 (&lt;941)</td>
<td>971 (&lt;919)</td>
<td>1577 (1041)</td>
<td>1203 (328)</td>
<td>855 (114)</td>
<td>0.0017</td>
</tr>
<tr>
<td>Right ABI</td>
<td>1.15</td>
<td>0.91</td>
<td>0.98</td>
<td>1.00 (0.10)</td>
<td>1.04 (0.10)</td>
<td>0.67</td>
</tr>
<tr>
<td>Left ABI</td>
<td>1.16</td>
<td>0.95</td>
<td>0.92</td>
<td>0.99 (0.10)</td>
<td>1.06 (0.10)</td>
<td>0.48</td>
</tr>
<tr>
<td>Averaged ABI (normal value for each age) [15]</td>
<td>1.16 (&gt;1.00)</td>
<td>0.93 (&gt;1.00)</td>
<td>0.95 (&gt;1.00)</td>
<td>0.99 (0.10)</td>
<td>1.06 (0.10)</td>
<td>0.54</td>
</tr>
</tbody>
</table>

CINCA syndrome: chronic infantile neurological cutaneous and articular syndrome; baPWV: brachial artery pulse wave velocity; ABI: ankle-brachial index.
Therefore it is reasonable to assume that the progression of atherosclerosis from childhood in three patients with CINCA syndrome is closely related to chronic systemic inflammation. It was reported that the incidence of atherosclerosis could be reduced by aggressive disease-modifying therapies in patients with RA and SLE [16]. In patients with CINCA syndrome, we can investigate the association between inflammation and atherosclerosis without any effect of classical risk factors such as obesity, smoking, hyperlipidaemia or diabetes. This may provide a novel clue to clarify the role of inflammation in the development of atherosclerosis.

In patients with FMF and SLE, age and disease duration were reported to be associated with the severity of atherosclerosis [17]. In the present study we found that the oldest patient (patient 3) with the longest disease duration had the most advanced atherosclerosis, which is in line with this report. Early diagnosis and effective treatment for chronic inflammation in these patients have been emphasized in preventing cardiovascular disease because a negative correlation between the duration of anti-inflammatory treatment and IMT has been observed in SLE patients [18].

Interestingly, improvements in PWV and cIMT [19] were reported in patients with RA after sufficient infliximab treatment. In patients with CINCA syndrome, canakinumab was reported to induce rapid and sustained remission of symptoms [20]. It is possible that a significant improvement in atherosclerosis will be observed in our patients with CINCA syndrome after canakinumab treatment in the near future.

However, there are some limitations in the present study. First, our study contains only a small number of patients because of the extremely rare incidence of this disease. Second, the parameters investigated in this study are considerably variable with the age of the subjects. It is also possible that the values of the parameters change because of the measurement equipment. Multicentre and long-term follow-up analysis with standardized procedures and tools on a larger number of the patients are necessary to provide more precise information on the pathogenesis of atherosclerosis.

Conclusion

Patients with CINCA syndrome developed atherosclerosis from early childhood. Atherosclerosis in CINCA syndrome patients may be a prototype of cardiovascular disease predominantly induced by chronic inflammation.

Acknowledgements

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Disclosure statement: The authors have declared no conflicts of interest.

References


Rheumatology key messages

- Patients with CINCA syndrome develop atherosclerosis from early childhood.
- This report shows the youngest group of patients who developed atherosclerosis associated with inflammatory disorders.
- Early treatment with anti-IL-1β antibody might be beneficial in preventing atherosclerosis in CINCA syndrome.


